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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,093	12/07/2006	Chikara Murakata	P29760	6880

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EXAMINER	
LOEWE, SUN JAE Y	
ART UNIT	**PAPER NUMBER**
1626	

NOTIFICATION DATE	DELIVERY MODE
09/04/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,093	MURAKATA ET AL.	
	Examiner	Art Unit	
	Sun Jae Y. Loewe	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *3,6,7,20-22,29-33 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,8-19,23-28,34-37 and 39-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/10/2007,4/10/2007,12/15/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I and compound 49 (specification page 46) in the reply filed on August 16, 2007 is acknowledged. The traversal is on the ground(s) that:

Joule et al. (Heterocylic Chemistry, 3rd edition, Chapman & Hall, 1972, page 452) teaches the common technical feature of the claims and stops at this point, failing to show how the claims of the present invention are anticipated or obvious over Joule et al. Thus, Applicants respectfully submit that the Restriction Requirement fails to comply with PCT Rule 13.1 and 37 C.F.R. § 1.475 for failure to make the proper showing.

This is not found persuasive for the following reasons.

The core structure common to all compounds instantly claimed is a thiadiazole ring. The substituents to the thiadiazole ring are variables that do not constitute common structures shared by all compounds claimed. Therefore, the inventions of Groups I-V do not relate to a single general inventive concept.

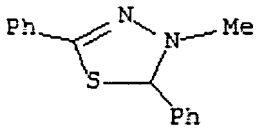
It is further noted that PCT Rule 13.1 does not require for a Markush alternative to be anticipated or made obvious by the prior art in order to establish lack of unity. Notwithstanding this statement, Applicant's argument does not apply in view of the rejection set forth in section 10.

The restriction requirement is still deemed proper and is therefore made FINAL.

2. Claims 3, 6, 7, 20-22, 29-33 and 38 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter. Applicant timely traversed the restriction (election) requirement in the reply filed on August 16, 2007.

3. MPEP § 803.02 provides guidelines for election of species in Markush-type claims. These guidelines were followed for the search and examination detailed herein.

The elected species appeared to be allowable over the art of record, therefore the search and examination was extended to the non-elected species of:



This compound was found to be anticipated by the prior art (below, Section 10), thus Markush-type claims were rejected and the subject matter drawn to nonelected species held withdrawn from further consideration.

Claims 1, 2, 4, 5, 8-19, 23-28, 34-37 and 39-56 were further examined, pursuant to MPEP § 803.02, to the extent necessary to determine patentability. The *search* was *limited* to the elected species and the non-elected species identified above.

It has been determined that the entire scope claimed is not patentable.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted (December 15, 2006; April 10, 2007; May 10, 2007) were in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statements were considered. Signed copies of form 1449 are submitted herewith. The references identified as #20 and #21 in the IDS dated April 10, 2007 were not considered because copies were not provided.

Claim Objections

5. Claims 1, 2, 4, 5, 8-19, 23-28, 34-37 and 39-46 objected to for containing non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(Written Description)

6. Claims 1, 2, 4, 5, 8-19, 23-28, 34-37 and 39-46 rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

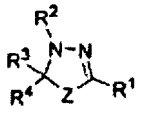
The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine

whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

I. *Scope of Claims*

Compounds of Formula I



The following variables are claimed *broader* than what is supported by the disclosure (see below section II):

Z:	for all claims *except* 25
R^1:	for all claims *except* 28
R^2:	for all claims *except* 11, 12 and 35
R^3:	for all claims *except* 15, 16 and 36
R^4:	for all claims *except* 42

II. *Scope of Disclosure*

Reduction to Practice:

The compounds reduced to practice support the following definitions for the variables noted above.

Z:	sulfur
R^1:	substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, $-C(=W)R^5$ wherein W=oxygen; R^5=hydrogen, alkyl furan, pyrazine, thiophene, pyrrole, indole phenyl
R^2:	$-C(=W^1)R^{12}$ [wherein W^1 represents an oxygen atom; R^{12}=hydrogen, alkyl]
R^3:	hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, phenyl and piperazine

R^4: phenyl

Reduction to Structural or Chemical Formulas:

The only disclosure, in addition to the species reduced to practice, is in form of *lists* of possible groups, for example:

pyrazolyl, triazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, pyrimidinyl, indolyl, isoindolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl, quinolyl, isoquinolyl, quinazolinyl, pyranyl, and the like. for heteroaryl.

This type of disclosure is not viewed to be a representation of any of the species it entails. A"laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Therefore, there is no disclosure of species (eg. by reduction to structural/chemical formulas) in addition to those reduced to practice.

Correlation between Structure and Function:

A correlation between structure and function, for the instantly claimed genus of compounds, is neither known in the art nor disclosed in the specification. Thus, it is not understood what *specific structural elements* are *essential* for the activity of the instantly claimed compounds inhibitors of Eg5.

III. *Analysis of Fulfillment of Written Description Requirement:*

The structure/activity relationship (SAR) for binding and activity is elucidated upon analysis of IC_{50} data of multiple compounds with various types of structural modifications. These types of studies provide insight into the structural limitations that are required for activity, ie. specific structural elements essential for the claimed activity. In the absence of such correlation, it is not possible to determine what structural modifications will allow for the preservation of the desired activity.

In conclusion: (i) substantial structural variation exists in the genus/subgenus embraced by claims 1, 2, 4, 5, 8-19, 23-28, 34-37 and 39-46; (ii) disclosure of species supporting genus is limited to compounds reduced to practice, which scope is not commensurate with the scope of genus/subgenus claimed; (iii) common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

(Enablement)

7. Claims 1, 2, 4, 5, 8-19, 23-28, 34-37 and 39-56 rejected under 35 U.S.C. 112, first paragraph. The specification is *enabling* for:

(a) The use of compounds with adequate written description

(b) Making/using agents for treatment (not including prophylaxis) of colon cancer

(c) Method of treating (not including prophylaxis) colon cancer

The specification is *not enabling* for:

(aa) The use of compounds without adequate written description

(bb) Making/using "antitumor agents" or "therapeutic agents for disease involving cell proliferation" or "mitotic kinesin Eg inhibitor"

(cc) Method of treating tumor, treating disease involving cell proliferation, inhibiting mitotic kinesin Eg5.

In conclusion, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8USPQ2s 1400, 1404 (Fed. Cir. 1988). MPEP 2164.01(a) states "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue". The factors are applied below to the instant claims.

The breadth of the claims

(aa) Compounds not supported by the disclosure (see above section 6.I and 6.II.).

(bb)-(cc) Process (or intended use for product) of treatment of tumor, treatment of disease involving cell proliferation, inhibiting Eg5. It is noted that tumors are encompassed by the definition of "diseases involving cell proliferation", instant specification page 3. It is also noted that in the broadest sense, absent specific definition, inhibition of Eg5 includes in vivo as well as in vitro inhibition.

The nature of the invention

(aa)-(cc) The compounds are disclosed to inhibit Eg5 in vitro (specification p. 50-51). The compounds are disclosed to have antiproliferative activity against human colon carcinoma cells (specification p. 49).

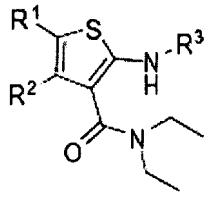
The state of the prior art/level of ordinary skill/level of predictability

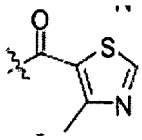
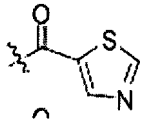
The level of ordinary skill is high, but the level of predictability in the art is low.

(aa) The compounds reduced to practice are disclosed to be inhibitors of Eg5. However, these compounds do not provide support for the full scope of the genus claimed (eg. R^1=aryl or heteroaryl/heterocyclic group). Structure-activity correlation studies (SAR) are not available for the instantly claimed genus of

compounds; such studies generally show what type of structural modifications/limitations are tolerated for activity towards a particular enzyme.

Furthermore, the level of predictability in the art is low. SAR studies, disclosed for different classes of Eg5 inhibitors, show that activity is highly dependent on chemical/structural parameters. For example, Pinkerton et al. (page 564, Table 1):



- Four fold decrease in activity upon modifying R^1 and R^2 from methyl to hydrogen
- Four fold decrease in activity upon modifying R3 from  to 

As discussed above, it is not known what structural limitations are required for preservation of activity within the genus claimed. In view of the low level of predictability (see example above), one of ordinary skill would not know what structural modifications within the unrepresented genus (ie. unrepresented by the disclosure), if any, would lead to compounds that are active. Thus, one of ordinary skill would not be enabled to practice the process of treatment claimed using compounds within the scope claimed for Formula I. One of ordinary skill would not be enabled to practice making/using agents with the intended uses claimed.

(bb)-(cc) Following is the state of the art for treatment/prevention/cure of tumor (including malignant tumor - cancer), which exemplifies disease involving cell proliferation:

- Anti-cancer drug research begins with in vitro evaluation with specific cancer cell cultures (Zips et al., p. 2 - Figure 1, page 3 - 1st paragraph). In vitro success does not necessarily translate to in vivo effect. For example, artificial culture conditions may not well represent the situation in vivo (Zips et al., p. 3, 2nd column, 2nd paragraph).
- Not all tumor cell lines show the same magnitude of response to anticancer agents; the underlying reasons for intertumoral heterogeneity are poorly understood (Zips et al., p.2, 2nd column, 1st paragraph).

- To cure a tumor, it is necessary to inactivate all clonogenic cells either by cell kill or by inducing a permanent state of dormancy (Zips et al., p.2, 1st column, 2nd paragraph); drugs like EGFR inhibitors (i.e. a protein kinase inhibitor) may inhibit proliferation without pronounced cell kill, i.e. clonogens proliferate more slowly but are not inactivated (Zips et al., p.3, column 1, 4th paragraph).
- Conclusions:
  - Success in treating one type of cancer (eg. colon) does not translate to success for treating a different type of cancer (eg. ovarian).
  - The prophylactic treatment of any type of tumor is unpredictable; therefore, absent a showing of prevention/cure it is not possible to predict whether prophylaxis will occur.

Following is the state of the art for Eg5 inhibition in vivo:

- In vitro Eg5 activity does not translate to in vivo activity (eg. DeBonis et al., p. 1082, Figure 1A)
- Multiple proteins are involved in mitosis. For example, Mayer et al. disclosed a study wherein 139 compounds were selected based on activity in increasing phosphorylation of nucleolin (suggestive of mitotic arrest) – page 972. Of this initial library, one compound was determined to inhibit microtubule movement via Eg5 inhibition.
- In conclusion, an in vitro/vivo correlation does not currently exist for Eg5 inhibition; further, observation of mitotic arrest does not necessarily correlate to Eg5 inhibition because multiple proteins may be involved.

The amount of direction provided by the inventor/existence of working examples

(aa)-(cc) No direction or working examples.

The quantity of experimentation needed to make or use the invention

(aa) It is not known which of the unrepresented compounds meet the structural requirements for activity. Thus, one of ordinary skill would not be enabled by the disclosure to practice the claimed invention, which relies on the ability of the compounds to be inhibitors of Eg5. The amount of experimentation needed to practice the invention is deemed to be undue.

(bb) Absent guidance and/or art recognized correlation between in vitro and in vivo activity, in view of the unpredictability in the art, one of ordinary skill is not enabled to practice the invention commensurate in scope with the claims. The amount of experimentation is undue.

(cc) Absent guidance and/or art recognized correlation between inhibition of Eg5 and the treatment of the full scope of the diseases claimed in view of the

unpredictability in the art, one of ordinary skill is not enabled to practice the claimed invention. The amount of experimentation is undue.

Claim Rejections - 35 USC § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 23-28, 34-37 and 39-56 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically these claims are drawn to "**thiadiazoline derivative**". The term "derivative" is defined usually as organic compounds obtained from another compound by a simple chemical process or an organic compound containing a structural radical similar to that from which it is derived (Hackh's chemical dictionary, 1972). Therefore, the term "derivative" renders the claims indefinite because it is unclear what compounds are being claimed. It is suggested to overcome this rejection, applicant amend the claims to limit the term "derivatives".

Claim Rejections - 35 USC § 101 and 35 USC § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claim 49, 50 and 54-56 provides for the use of the compounds for the manufacture of products. Because the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it

merely recites a use without any active, positive steps delimiting how this use is actually practiced.

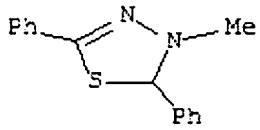
Claims 49, 50 and 54-56 rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 2, 4, 5, 8, 17-19, 23-28 and 39-46 rejected under 35 U.S.C. 102(b) as being anticipated by Holmberg (RN 859460-84-7).



Z=sulfur; R^1=unsubstituted aryl; R^2=unsubstituted alkyl; R^3=hydrogen; R^4=unsubstituted aryl.

Conclusion

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sun Jae Y. Loewe whose telephone number is (571) 272-9074. The examiner can normally be reached on M-F 7:30-5:00 Est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sun Jae Y. Loewe, Ph.D.
Art Unit 1626